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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,324	TISSENBAUM ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-9,14-26,33-45 and 48-56* is/are pending in the application.

4a) Of the above claim(s) *49-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-9,14-26, 33-45 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Formal Matters

Claims 1, 4, 7, 9, 14, 15, 24-26, 33 and 45 are amended. Claim 2 is cancelled. Claims 8 and 49-56 are withdrawn from consideration. Claims 1, 4, 7, 9, 14-26, 33-45 and 48 are under examination.

Rejections/Objection Withdrawn

The rejections of claim 2 as set forth in the Office action mailed 11 February 2009 are withdrawn due to Applicants' cancellation of that claim.

Claim Objections

The objection to claim 48 to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim as set forth at p. 3 of the Office action mailed 11 February 2009 is withdrawn in response to Applicants' explanation at p. 10, penultimate paragraph of their Remarks.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claim 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth at p. 4 of the previous Office action is

withdrawn in response to Applicants' amendment of claim 33 to depend from claims 25 or 26 instead of claim 24. Claims 25 and 26 both mention the insulin signaling pathway.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The rejection of claims 4, 9, 14-26, 33-45 and 48 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as set forth at p. 4-6 of the Office action mailed 11 February 2009 is withdrawn in response to Applicants' argument and explanation at p. 11 of their Remarks. The explanation includes a thorough compilation of the teachings of the specification, providing evidence of written description of "mammalian orthologue" in the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 14, 24, 33, 34, 36, 38 and 39 under 35 U.S.C. 102(b) as being anticipated by Pasricha (1994. Gut 35:1319 – 1321; of record) as set forth at pages 11-14 of the Office action mailed 11 February 2009 is withdrawn in response to Applicants amendment of the independent claims deleting reference to the SNARE complex. Pasricha teach administration of botulinum toxin, which acts by cleaving the SNARE proteins, but since the SNARE complex has been deleted from the claims, they are no longer encompassed by the teachings of Pasricha.

The rejection of claims 14 and 24 under 35 U.S.C. 102(b) as being anticipated by Dunant et al. (1990. J. Physiol. Paris 84:211-219; of record) as set forth at pages 14-17

is withdrawn in response to Applicants amendment of the independent claims deleting reference to the SNARE complex. Dunant et al. teach methods of administering botulinum toxin, which acts by cleaving the SNARE proteins, but since the SNARE complex has been deleted from the claims, they are no longer encompassed by the teachings of Dunant et al.

The rejection of claims 45 and 48 under 35 U.S.C. 102(b) as being anticipated by Richardson et al. (Molecular Pharmacology, 1991; 40:908-914; of record) as set forth at pages 17-18 is withdrawn upon reconsideration and investigation of the literature. Applicants argue that Richardson does not teach assays using the mammalian orthologues of EGL-30 (mammalian G protein Gq alpha), EGL-3 (mammalian PC2) and RIC-8 (mammalian synebryn) recited in the claims. This argument is persuasive.

The rejection of claims 45 and 48 under 35 U.S.C. 102(b) as being anticipated by Gusovsky et al. (European J Pharmacol. 1991; 206: 309-14) as set forth at pages 18-19 is withdrawn upon reconsideration and investigation of the literature. Applicants argue that Richardson does not teach assays using the mammalian orthologues of EGL-30 (mammalian G protein Gq alpha), EGL-3 (mammalian PC2) and RIC-8 (mammalian synebryn) recited in the claims. This argument is persuasive.

Maintained Objection/Rejections/New Rejection

Claim Objections

The objection to claim 45 as set forth at p. 3 of the Office action mailed 11 February 2009 for informalities is maintained. Although Applicants have amended the claim to correct "cell-fee" at the end of the third line, the claim now recites "contacting cell free-assay **a**" in the beginning of third line, and presumably the article "a" should precede "cell free-assay." Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites "said signaling pathway molecule", which is indefinite, since line 2 recites "cholinergic pathway molecule". Applicants have amended claim 1 to recite both the "cholinergic pathway" and the "insulin signaling pathway", thus it is not clear whether "said signaling pathway molecule" in claim 4 refers to the cholinergic or insulin signaling pathways.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

(i) The invention is complex. The method is drawn to identifying an agent capable of extending the mature life phase of an organism, the method comprising: contacting a cell-free assay composition with a test agent in vitro, wherein said cell-free assay composition comprises a cholinergic pathway molecule selected from the group consisting of EGL-30, EGL-3 and RIC-8, or a mammalian orthologue of said cholinergic pathway molecule; assaying for the ability of the test agent to affect the activity or expression of said cholinergic pathway molecule; and selecting an agent that inhibits the activity or expression of said cholinergic pathway molecule; to thereby identify an

agent capable of extending the mature life phase of an organism, wherein said assay composition is a cell-free extract. The specification does not disclose how a method showing that a test agent has an effect on EGL-30, EGL-3 or RIC-8 in a cell free system would be predictive of extending the mature life phase of an organism. Further, extending mature life phase in an organism is a complex issue. It is not clear how one skilled in the art could use the claimed methods to predict the ability of a test agent to extend adult life by extrapolation from a cell free assay.

(ii) The specification does not disclose any cell free assays or cell free extracts which contain EGL-30, EGL-3 or RIC-8 capable of being used for identifying agents capable of extending life. There is no guidance or working examples provided in the specification. The only reference to cell free assays, for example, at paragraph [0147] of the PGPUB, describes them in the context of an "agent being tested for its ability to modulate activity or expression of a neurotransmitter signaling pathway molecule." Nevertheless, there is no guidance provided to show one skilled in the art how to use a cell free assay to extrapolate how an agent extends adult lifespan. Furthermore, no guidance is provided by the inventor as to how one skilled in the art could monitor the activity or expression of a cholinergic pathway molecule (EGL-30, EGL-3, RIC-8) in a cell-free assay. Unlike the nematode, *C. elegans*, which is an art-accepted model for use in longevity assays, there is no corresponding description of a cell-free assay capable of being used to study longevity or adult lifespan.

(iii) Moreover, just as the specification provides no guidance, there is no corresponding guidance in the literature as to how the skilled artisan may use a cell free

assay as required by the claims to identify agents capable of extending adult lifespan. In short, the art is silent with respect to a cell free assay that can be used to identify agents capable of extending adult lifespan. Thus, it is the Examiner's reasoned belief that the state of the art is unpredictable regarding claims 45 and 48.

Due to the large quantity of experimentation necessary to identify and/or generate a cell free assay to be used to identify agents capable of extending the adult lifespan of an organism, the lack of direction/guidance presented in the specification regarding the same, and the absence of working examples directed to same, the complex nature of the invention, the unpredictable state of the art, (the level of skill of those in the art), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 14-22, 24-26, 33-36, 38 and 39, 40, 41-44 under 35 U.S.C. 102(b) as being anticipated by Ruvkun et al. (US Patent Application publication 2001/0029617, of record) as set forth at pages 6-11 is maintained for reasons of record and the following. ***In addition, it is noted that claims 41-44 should have been included in this rejection in the Office action mailed 11 February 2009. In order to***

give Applicants the opportunity to respond, this action is made non-final. Briefly, claim 41 is anticipated because *C. elegans* contain both pre- and post-synaptic cells; Ruvkun discusses synaptic signaling at paragraphs [0207] and [0212], for example. Claims 42-43 are anticipated because acetylcholine is used as a transmitter between neurons in *C. elegans* (see, for example paragraph [0163]). Claim 44 is anticipated because *C. elegans* also comprise muscle cells, but rather refers to which cells are present in the "cell population" of claim 41. The amended claims are drawn to a method for identifying an agent capable of extending the mature life phase of an organism, comprising contacting an organism having a cholinergic pathway and an insulin signaling pathway; assaying for the ability of the test agent to inhibit the cholinergic pathway by monitoring the effect of the test agent on one or more of the expression, intracellular level, extracellular level, activity, post-translational modification, interaction or cellular localization of an indicator of said cholinergic pathway as compared to a suitable control, wherein the indicator of said cholinergic pathway is selected from the group consisting of, among other things, muscarinic receptor, and selecting an agent that inhibits the cholinergic pathway, to thereby identify an agent capable of extending the mature life phase of an organism, or alternatively, or alternatively monitoring the effect of the test agent on indicators of both the cholinergic pathway molecule and the insulin pathway molecule, to thereby identify an agent capable of extending the mature life phase of an organism.

Applicants argue at p. 12, 3rd and 4th paragraphs that they have amended the claims to recite a method of identifying an agent capable of extending the mature life phase of an organism and that in contrast Ruvkun et al. teach methods of identifying

agents that modulate dauer formation, which is a dormant larval phase of *C elegans*, but nothing useful in extending the lifespan of an adult organism.

This argument has been fully considered but is not found persuasive for the following reasons. As noted in the Conclusion at p. 34 of the previous Office action, Tatar and Yin (of record) discuss the relevance of the study of dauer formation in *C elegans* as relevant to the study of aging and senescence; note particularly p. 730, 1st paragraph: "but while dauer is a juvenile-specific train, some daf-mutants also express adult phenotypes; many substantially extend adult longevity." Claims 12-15 of Ruvkun et al. recite a method for identifying a compound that is capable of increasing longevity of a cell or organism, comprising contacting a biological sample with a candidate compound and assaying said sample for PTEN-mediated lipid phosphatase activity (wherein PTEN is the mammalian ortholog of DAF-18), and wherein an increase in said activity indicates a compound capable of increasing longevity of a cell or organism, wherein said method further comprises assaying said compound in a cell which comprises a mutation in a daf-18 gene. Ruvkun et al. further discusses the significance of insulin signaling pathway molecules DAF-2, AGE-1, DAF-18 (and others) and their mammalian homologs at paragraphs [0008] – [0011]. At paragraphs [0162] - [0163] and Figure 46, Ruvkun et al. clearly indicate that the insulin signaling pathway is immediately downstream of the cholinergic pathway. Specifically, they teach that in the absence of muscarinic stimulation, no insulin like signal is released, whereas binding of acetylcholine to the receptor causes release of an insulin-like DAF-2 ligand and insulin release associated with dauer recovery. Furthermore, at paragraph [0165], Ruvkun et al. indicate that daf-2 mutant organisms undergo dauer arrest during the larval stage,

but also have dramatically increased adult longevity, thus Ruvkun et al. demonstrate not only the relationship between the cholinergic (muscarinic receptors) and insulin signaling pathways (DAF-2 signaling), but also the importance of DAF-2 signaling on lifespan (since the daf-2 mutants have increased lifespan). Further, at paragraphs [0406] – [0409], Ruvkun et al. demonstrate that antagonism of muscarinic receptors (i.e., an indicator of the cholinergic pathway) prevents the termination of the dauer stage, which is a stage characterized by the organism's ability to live for extended periods of time. Conversely, they teach at paragraph [0398] the "muscarinic [dauer] recovery pathway depends on insulin-like signaling. Atropine [a muscarinic antagonist] specifically inhibits dauer recovery." Ruvkun et al. teach at paragraph [0443] that the "insulin signaling pathway has been implicated in longevity control of *C elegans*. Drugs which perturb this pathway could affect lifespan. Specifically, inhibition of the pathway would be expected to extend lifepsan." It is intrinsic to the teachings of Ruvkun et al. that disruption of insulin signaling, which is caused by muscarinic antagonists, would extend the adult lifespan of *C elegans*. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency) (MPEP 2112).

Applicants argue at p. 12, 4th paragraph that Ruvkun et al. do not teach or suggest methods of identifying inhibitors of the EGL-30, EGL-8, RIC-8, DAG, SNARE complex and UNC-13 components of the cholinergic pathway.

Applicants' argument has been fully considered but is not found persuasive for the following reason. There is no requirement in the claims that inhibitors of only the EGL-30, EGL-8, RIC-8, DAG, SNARE complex and UNC-13 components of the cholinergic pathway be taught, since the claims also recite "muscarinic receptors" as a possible indicator of the cholinergic pathway. As noted in the immediately preceding paragraphs, Ruvkun et al. do teach inhibition of the muscarinic receptors by atropine.

Claim Rejections - 35 USC § 103

Note, in this section Arguments will be addressed after the Rejections, since Applicants discussed the rejections under 35 U.S.C. 103(a) together in their Remarks.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1, 4, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record), and further in view of Gems & Riddle (Genetics, 2000; 154: 1597-1610) as set forth at pages 19-24 in the Office action mailed 11 February 2009 is maintained for reasons of record and the following. ***In addition, due to the amendment that now includes an alteration of activity or expression of UNC-13, claim 4 is now captured by the prior art teachings, and is hereby included in this rejection***. The claims are drawn to a method for identifying an agent capable of extending the mature life phase of an organism comprising contacting an organism having altered activity or expression of a cholinergic pathway molecule and altered expression of an insulin signaling pathway molecule with a test agent, wherein said altered activity or expression of a cholinergic pathway or said altered activity or expression of the insulin signaling pathway molecule extends the mature life phase of the organism, assaying for the ability of the test agent to increase the lifespan of the organism with respect to control, selecting an agent that increases the lifespan, to thereby identify an agent capable of extending the mature life phase of an organism, wherein said organism also has altered activity or expression of an insulin signaling pathway molecule selected from the group consisting of DAF-2, AAP-1, IRS, AGE-1 PDK-1, AKT-1, AKT-2 DAF-16 and DAF-18 or a mammalian orthologue thereof.

The rejection of claim 23 under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record) as applied to claims 14, 21-22, 24-26, 33-36, 38 and 39, 40 as set forth at pages 24-25 of the Office action mailed 11 February 2009 is maintained for reasons of record and the following. The reasons why claims 14, 21-22, 24-26, 33-36, 38 and 39, 40 are anticipated by Ruvkun et al. are set forth in the rejection under 35 USC 102 above. Ruvkun et al. also teach using the parasitic nematode *A. caninum* in different screening assays such as for finding nematicides and teaches the similarity of the biochemical pathways in *C. elegans* and *A. caninum*, and thus is on point to claim 23, but do not explicitly not disclose carrying out the longevity screening assays in the parasitic nematode, *A. caninum*.

The rejection of claims 20 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruvkun et al. (US Patent Application 2001/0029617; of record) as applied to claims 1, 2, 4, 7, 9, 14-19, 21-22, 24-26, 33-36, 38 and 39-44 as set forth at pages 25-26 of the Office action mailed 11 February 2009. The reasons why claims 1, 2, 4, 7, 9, 14-19, 21-22, 24-26, 33-36, 38 and 39-44 are anticipated by Ruvkun et al. are set forth in the rejection under 35 USC 102 above. Ruvkun also et al. teach screening assays with the scope of those claims using the nematode *C. elegans* at paragraph [0165], Ruvkun et al. indicate that daf-2 mutant organisms undergo dauer arrest during the larval stage, but also have dramatically increased adult longevity. Ruvkun et al. also teach that when performing other screening assays, agents can be identified based on

their ability to alter sub-cellular localization of indicators such as GFP fusion proteins (see for example paragraphs [0242], [0319] - [0326], and [0421]).

Response to Arguments under 35 U.S.C. 103(a)

Applicants argue at p. 14, last paragraph, that with respect to the cholinergic pathway, Ruvkun et al. only teach assays monitoring the ability of muscarinic agonists to induce or inhibit the recovery of DAF mutants from the constitutive dauer state.

This argument has been fully considered but is not found persuasive. Ruvkun et al. teach at paragraphs [0406] – [0409] that antagonism of muscarinic receptors (i.e., an indicator of the cholinergic pathway) prevents the termination of the dauer stage, which is a stage characterized by the organism's ability to live for extended periods of time. Conversely, they teach at paragraph the "muscarinic [dauer] recovery pathway depends on insulin-like signaling. Atropine [a muscarinic antagonist] specifically inhibits dauer recovery." Further, Ruvkun et al. clearly suggest at paragraphs [0443] – [0445] how the "insulin signaling pathway is implicated in longevity control [and that] [d]rugs that perturb this pathway could affect lifespan." As explained above, Ruvkun et al. teach the effects of DAF-2 signaling on lifespan (since the daf-2 mutants have increased lifespan), thus they recognized the effect of this insulin signaling pathway molecule on lifespan. Furthermore, Ruvkun et al. recognized the connection between the cholinergic and insulin signaling pathways. Even though Ruvkun et al. do explicitly not disclose that the altered expression or activity of the cholinergic pathway molecule leads to increased lifespan, Gems and Riddle teach mutations in pathway molecules that lead to increased lifespan, including unc-13 (see, for example, p. 1601; also Figure 4; thus encompassing

amended claim 4). In summary, Ruvkun et al. clearly teach that 1) muscarinic receptor (cholinergic pathway) inhibition disrupts the insulin signaling pathway; 2) insulin signaling is implicated in longevity control and its disruption would extend longevity; 3) assays testing for drugs that disrupt insulin signaling would increase longevity, and Gems and Riddle corrects the deficiency in Ruvkun et al. by suggesting genes in the cholinergic pathway that affect longevity.

Applicants argue at p. 14, last paragraph that Ruvkun et al. neither teach nor suggest that methods of identifying agents capable of extending the mature life phase of an organism by assaying an organism having an altered cholinergic ***and*** insulin signaling pathway as presently claimed.

This argument has been fully considered but is not found persuasive. As noted in the immediately preceding paragraph, Ruvkun et al. clearly teach that 1) muscarinic receptor (cholinergic pathway) inhibition disrupts the insulin signaling pathway; 2) insulin signaling is implicated in longevity control and its disruption would extend longevity; 3) assays testing for drugs that disrupt insulin signaling would increase longevity, and Gems and Riddle corrects the defect in Ruvkun et al. by suggesting genes in the cholinergic pathway that affect longevity. The person of skill in the art is presented with the blueprint of a longevity screening assay in Ruvkun et al. along with the vital information of how the cholinergic and insulin signaling pathways are connected. After reading Ruvkun et al., and upon reading Gems and Riddle, the person of ordinary skill in the art would recognize that disruptions of gene expression in the both the cholinergic and insulin signaling pathways leads to greater adult longevity.

Applicants argue at p. 15, 1st paragraph that none of the muscarinic agonists and antagonists discussed by Ruvkun et al. could induce dauer recovery of daf-2 mutants.

This argument has been fully considered but is not found persuasive. Ruvkun et al. teach that gene disruptions in the insulin signaling pathway lead to increased dauer arrest and adult longevity (for example, see paragraph [0165], where Ruvkun et al. indicate that daf-2 mutant organisms undergo dauer arrest during the larval stage, but also have dramatically increased adult longevity). In other words, the increased length of dauer arrest is associated with adult longevity in these animals. Therefore, it is not clear to the Examiner how inducing dauer recovery (i.e., ending dauer arrest) in daf-2 mutants would be evidence of increasing adult lifespan. On the contrary, the fact that muscarinic agonists did not induce dauer recovery of daf-2 mutants appears to be strong evidence of the resistance of these animals to cholinergic and insulin signaling stimulation. For example, see paragraph [0413]:

> The lack of muscarinic [i.e. cholinergic pathway] induced dauer recovery in daf-2 mutants suggest that the insulin-like dauer recovery signal acts via the DAF-2 receptor homologue. From analogy with the vertebrate studies, we suggest that a muscarinic signal causes an increase in insulin release that would bind to the DAF-2 receptor and activate downstream genes which promote dauer recovery.

In other words, the fact that the muscarinic agonists could not induce dauer recovery of daf-2 mutants is evidence linking the interrelationship of the muscarinic and insulin signaling pathways, and that disruption of one or both leads to increased dauer arrest and in the case of daf-2 mutants, adult lifespan.

Applicants argue that Gems and Riddle fail to cure the deficiencies of Ruvkun et al. as they disclose single mutations that affect longevity in male, but does not teach nor suggest assays for identifying agents that affect the length of the adult lifespan in an organism containing altered expression or activity of a molecule in both the cholinergic and insulin signaling pathway.

This argument has been fully considered but is not found persuasive. Ruvkun et al. teach the strong interrelationship between the cholinergic and insulin signaling pathways (see for example paragraph [0413]) and how 1) muscarinic receptor (cholinergic pathway) inhibition disrupts the insulin signaling pathway; 2) insulin signaling is implicated in longevity control and its disruption would extend longevity; 3) suggests that assays testing for drugs that disrupt insulin signaling would increase longevity. The only deficiency in Ruvkun et al. is that they do not specifically teach what cholinergic pathway gene alterations result in increased lifespan. Gems and Riddle corrects the deficiency in Ruvkun et al. by suggesting genes in the cholinergic pathway that affect longevity by increasing adult lifespan. Furthermore, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

Claims 1, 4, 7, 9, 14-26 and 33-45 and 48 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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